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## **Roche to commence phase III trials with innovative treatment designed to lower cardiovascular risk in diabetes patients with recent heart attack**

### **SYNCHRONY study published in *The Lancet* supports cardio-protective potential of aleglitazar**

Roche today announced it will start Phase III clinical investigations for aleglitazar, its innovative PPAR co-agonist R1439 which is uniquely designed to reduce cardiovascular morbidity and mortality in high risk patients with type 2 diabetes. This decision is supported by data from the Phase II SYNCHRONY study published today in *The Lancet*<sup>1</sup> and announced at the American Diabetes Association (ADA) in New Orleans, US. The phase III programme is anticipated to start in the second half of 2009.

SYNCHRONY, a placebo-controlled dose ranging study in type 2 diabetes patients, showed that aleglitazar had a balanced synergistic effect on both lipid and glucose control with a good safety and tolerability profile in patients with type 2 diabetes.

Cardiovascular disease is currently the leading cause of death amongst those with type 2 diabetes, accounting for half of all deaths.<sup>2</sup> Despite guidelines recommending that cardiovascular risk in this patient group should be reduced by controlling factors such as dyslipidemia, blood pressure, body weight and hyperglycaemia,<sup>3,4</sup> the majority of patients still do not achieve their treatment goals leaving them vulnerable to both initial and residual cardiovascular events.<sup>3,5</sup> Significantly, one in ten people experiencing an Acute Coronary Syndrome (ACS) dies within a year.<sup>6</sup>

“Roche is confident that aleglitazar has the potential to reduce cardiovascular morbidity and mortality in this high-risk patient group and is therefore committed to pursuing its rapid development.” said Jean-Jacques Garaud, Global Head of Development Pharmaceuticals Division of Roche.

The focused phase III outcomes trial will investigate whether once daily 150µg aleglitazar reduces the incidence of cardiovascular mortality, non-fatal myocardial infarction and stroke in patients with type 2 diabetes. The approach in this selected high-risk patient population will be unique as no drug has been demonstrated to reduce cardiovascular risk in Type 2 diabetes patients following an ACS event.

Professor Robert Henry, SYNCHRONY Clinical Investigator and Chief VA Endocrinology & Metabolism and Professor of Medicine in Residence at the University of California at San Diego, US commented: “The favourable balance in the safety and efficacy profile of aleglitazar seen in the SYNCHRONY study represents encouraging short-term clinical data for this agent and provides good evidence to enter phase III investigation.”

With the decision to move into Phase III, aleglitazar is Roche’s third phase III clinical trial programme in the area of metabolism. The new Phase III study is a cardiovascular outcomes trial designed to assess the potential of once daily 150µg aleglitazar to reduce cardiovascular mortality, non-fatal myocardial infarction and stroke in Type 2 diabetes patients with a recent Acute Coronary Syndrome.

### **About the SYNCHRONY study**

SYNCHRONY was a multicentre, randomised, double-blind, placebo-controlled dose ranging study amongst 332 type 2 diabetes patients (either drug-naïve or pre-treated with ≤2 oral agents). Designed to determine the glucose-lowering and lipid-modifying effects, and safety profile of aleglitazar, the study confirmed the favorable safety and efficacy profile of the once daily 150µg aleglitazar dose and supported commencement of the phase III clinical investigation.

Patients underwent a single-blind 4- to 5-week placebo run-in period, then were randomised to receive 16 weeks’ treatment with either aleglitazar at one of four once daily doses (50, 150, 300 or 600µg), placebo or 45mg pioglitazone.

The primary endpoint of dose-dependent reductions from baseline HbA1c versus placebo was met and a range of responses observed from -0.36% (95% CI:0.00 to -0.70, P=0.048) with 50µg aleglitazar, to -1.35% (95% CI: -0.99 to -1.70, p<0.0001) with the 600µg dose. Notably the once daily 150µg aleglitazar dose (currently in clinical trials) demonstrated numerically comparable reductions from baseline HbA1c to those observed with pioglitazone (-0.85%, 95% CI: -0.50 to -1.20, P<0.0001 vs.-0.71%, 95% CI: -0.36 to -1.06, P<0.0001).

The study’s secondary clinical endpoints were change from baseline in fasting plasma glucose and lipid profiles. Notably, significant dose-dependent reductions versus placebo were observed with aleglitazar for fasting plasma glucose (-1.0 mmol/L with 50 µg to -3.3 mmol/L with 600 µg), triglycerides (-27.8% with 50µg

to -51.6% with 600µg), and LDL-C (- 9.1% with 50 µg to -25.9% with 600 µg), as well as a significant dose-dependent increase in HDL-C (8.2% with 50 µg to 22.9% with 300µg). Significantly, treatment with the once daily 150µg aleglitazar dose produced a numerically superior effect on triglycerides, HDL-C, and LDL-C when compared with 45mg pioglitazone.

Known PPAR- $\alpha$  (creatinine increase) and  $\gamma$ -related effects (oedema, haemodilution, and weight gain) were seen in a dose-dependent manner of which the incidence of oedema was similar to placebo and less than with pioglitazone, and body weight gain was less than with pioglitazone.

### **About Aleglitazar**

Aleglitazar is an innovative investigational treatment designed to reduce the incidence and impact of cardiovascular mortality, non-fatal myocardial infarction and stroke in patients with a recent Acute Coronary Syndrome and type 2 diabetes.

It is a rationally designed molecule providing balanced dual PPAR  $\alpha/\gamma$  activation. Specifically it combines the improvements in peripheral insulin sensitivity (and therefore glycemic control) associated with PPAR  $\gamma$  activation, with improved management of dyslipidemia, which is commonly associated with PPAR  $\alpha$  activation. Aleglitazar is now entering phase III clinical trials.

### **About Diabetes**

Diabetes is a disease characterised by excess blood glucose due to a deficiency in insulin availability and/or resistance to its action. Type 2 diabetes accounts for 90 percent of all diabetes cases worldwide.<sup>2</sup>

Complications from diabetes, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness, are resulting in increasing disability, reduced life expectancy and enormous health cost for virtually every society.<sup>2</sup> According to current estimates by the World Health Organization, more than 180 million people worldwide have diabetes.<sup>2</sup> This number is likely to more than double by 2030.<sup>2</sup>

### **About Roche**

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company with truly differentiated medicines in oncology, virology, inflammation, metabolism and CNS. Roche is also the world leader in in-vitro diagnostics, tissue-based cancer diagnostics and a pioneer in diabetes management. Roche's

personalised healthcare strategy aims at providing medicines and diagnostic tools that enable tangible improvements in the health, quality of life and survival of patients.

In 2008, Roche had over 80'000 employees worldwide and invested almost 9 billion Swiss francs in R&D. The Group posted sales of 45.6 billion Swiss francs. Genentech, United States, is a wholly owned member of the Roche Group. Roche has a majority stake in Chugai Pharmaceutical, Japan. For more information: [www.roche.com](http://www.roche.com).

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<sup>1</sup> Henry R et al. The dual peroxisome proliferator-activated receptor  $\alpha/\delta$ : results from SYNCHRONY, a phase II, randomised, dose-ranging study in patients with type 2 diabetes. *The Lancet*, online edition, 8 June 2009

<sup>2</sup> World Health Organisation. Diabetes Fact Sheet No 312, November 2008

<sup>3</sup> American Diabetes Association. Standard of medical care in diabetes – 2008. *Diabetes Care* 2008; 31 Suppl 1: S12-54

<sup>4</sup> Graham I et al. European Guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Eur heart J* 2007; 28: 2375-414

<sup>5</sup> Saydah SH et al. poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004; 291: 335-42

<sup>6</sup> Montalescot G and al. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). *Eur Heart J* 2007; 28: 1409-1417